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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/642,272 | 08/18/2003 | Fumiyuki Hattori | 58777.000012 | 3248 |

21967 7590 05/17/2007

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|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 05/17/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/642,272 | HATTORI ET AL. | |
| | Examiner | Art Unit | |
| | Marcia S. Noble | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *09 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,7,8 and 14-38* is/are pending in the application.

4a) Of the above claim(s) *15-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8,14 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/10/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Claims*

1. Claims 1, 7, 8, and 14-38 are pending. Claims 15-32 were previously withdrawn in the Office Action mailed 8/9/2006. Claims 1 and 8 are amended, claims 2-6 and 9-13 are canceled, and claims 33-38 are added by the amendment filed 2/9/2007. Claims 1, 7, 8, and 33-38 are under consideration.

### *Information Disclosure Statement*

2. The information disclosure statements (IDSs) filed 4/10/2007 and 2/9/2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The information disclosure statement filed 3/14/2007 was a duplicate of the IDS filed 4/10/2007 and therefore, it was crossout.

### *Sequence Compliance*

3. The sequence disclosure on page 37, line 1 of the specification recited an amino acid sequence that did not have a SEQ ID NO: that corresponded to the CRF and Sequence Listing, and therefore did not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

An amendment to the specification to correct this amino acid sequences disclosure was filed 2/9/2007 and therefore is now in compliance with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

***Specification***

4. The use of the trademark Taqman® on p. 38, [00123] and p. 46, [00141], and THERMO Sequences™, on p. 39, [00126], has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The trademarks were corrected in the amendment to the specification filed 2/9/2007.

***Claim Objections***

5. Claims 1 and 2 are objected to because of the following informalities: Claims 1 and 2 recite, "transfecting a nucleic acid". However, nucleic acids are not transfected. Cells are transfected with nucleic acids.

Claim 1 is further objected to for not reciting what is being transfected with a nucleic acid (eg- a cell, a mouse, a human, etc...).

Appropriate correction is required.

Applicant amended the claims and claims 1 and 2 no longer encompass this recitation. Therefore the objection is withdrawn.

***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

6. The objection of claim 14, under 37 CFR 1.75 as being a substantial duplicate of claim 8, is withdrawn.

Applicant suggests that this objection is improper because claim 7 further limits the disease to be treated. Applicant's arguments are found persuasive and therefore, the rejection is withdrawn.

7. The objection of claim 7, under 37 CFR 1.75 as being a substantial duplicate of claim 1, is withdrawn.

Applicant suggests that this objection is improper because claim 7 further limits the disease to be treated. Applicant's arguments are found persuasive and therefore, the rejection is withdrawn.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Written Description***

7. The rejection of claim(s) 1-14, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn.

Applicant amended the claims to recite a nucleic acid encoding AOP-1 or a nucleic acid that hybridizes under stringent conditions to a complementary strand of a nucleic acid encoding AOP-1 and encodes a polypeptide that retains the function of AOP-1. The specification provides adequate written for this recitation. Therefore, the rejection is withdrawn.

***Scope of Enablement***

8. Amended and original claims 1, 7, 8, and 14 stand rejected and new claims 33-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating chronic heart failure comprising administering to the heart of a rodent by direct cardiac injection or catheter-based delivery, a vector comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said nucleic acid encoding AOP-1 in the heart of said rodent and while being enabling for a therapeutic agent for treatment of chronic heart failure comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said AOP-1 nucleic acid in the heart and wherein said nucleic acid enhances the expression and production of AOP-1, does not reasonably provide

enablement for a prophylactic or therapeutic agent for a disease associated with decreased AOP-1 gene expression comprising: (1) transfecting cell of any affected tissue with any nucleic acid encoding AOP-1 or a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 by any means of delivery or (2) administering a material enhancing the expression of an/the AOP-1 gene, the production of AOP-1, or the function of AOP-1 by any means of delivery and does not reasonably enable a prophylactic or therapeutic agent for any disease associated with decreased expression of AOP-1 gene or AOP-1, comprising (1) any nucleic acid encoding AOP-1 or (2) any material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1 as set forth on pages 10-20 of the Office Action, mailed 8/9/2007.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discloses the purpose of the instant invention is to provide methods of preventing or treating diseases associated with decreased expression of AOP-1 gene or protein (p. 6, [0011]). The specification provides in vitro evidence that that cardiac myocytes transfected with AOP-1 are provided protection by AOP-1 against damage and loss of cell viability induced by hypoxia and reperfusion following hypoxia (p. 41-42, [00132]). The specification also provides a method of delivering an adenoviral vector encoding a AOP-1 gene, operably linked to a CMV promoter and a poly A signal from bovine growth hormone (p. 40, [00127]), to the left ventricle of the heart via a catheter in a chronic hear disease rodent model (p. 48, [00151]). AOP-1 gene delivery to the heart resulted in significantly better functional recovery during reperfusion following induced ischemic attach. The time from ischemia to ischemic rigidity was significantly extended in the AOP-1 treated heart compared to sham controls. Also, LDH release, a marker correlated with cell injury and necrosis, was significantly repressed in the AOP-1 treated group compared to controls (p. 49, [00153]).

The art teaches that in vivo cardiac gene delivery to rodents is feasible by direct injection or catheter-based delivery using viral vectors (Hajjar et al PNAS 95:5251-5226,

1998) and also demonstrated its use in cardiac disease and heart failure rodent models (del Monte et al. Circulation 104:1424-1429, 2001). However, at the time of filing, the art of gene therapy for cardiac disease was premature for clinical use and many obstacles would need to be overcome before human trials were possible (Hajjar et al. Circ Res 86:616-621, 2000).

Tomasoni and Benigni (Current Gene Therapy 4: 115, col 1 lines 4-7) state, "the success of gene therapy largely depends on an efficient delivery system for the transfer and expression of the therapeutic gene in the target organ or tissue." Many forms of vector delivery to a body site have been described in the art, but very few predictably deliver a therapeutic dose of a vector to the site of treatment. Gautam et al (Am J Respir Med, 1(1) abstract) discloses the use of different vector delivery routes to the lung, such as intravenous injection, intratracheal installation, and aerosol with varying degrees of success. They further disclose various barriers to delivery of vectors such as serum proteins during intravenous injection, surfactant and mucus interference during more topical applications of vectors. There has also been the problem of immune and cytokine responses against the vector delivery vehicle obstructing delivery of gene therapies. Adenoviral vectors have been problematic in their use for gene therapy due to their immunogenic properties and natural tropism for hepatocytes (Gunther et al, Curr Med Chem – Anti-Cancer Agents, 5:p. 157, col 2, par 2, lines 14-17 to p. 158, col1 par 1, lines 1-3). Therefore, these problematic factors of immune response and alternative tropisms of the vectors preclude the delivery of these vectors by other means than direct administration to the target site.

In terms of specific delivery to the heart, Hajjar et al teaches, "...the vector must be delivered to the affected tissues. This poses a particularly formidable barrier in conditions with an extensively distributed phenotype [p. 617, col 1, par 2, lines 11-14]...direct injection of adenovirus into the ventricular wall using an epicardial approach has also been shown to include significant expression of reporter constructs, however, the expression was focal, and the injections with the myocardium caused needle damage. Intramyocardial delivery of adenovirus using an intraventricular approach with retroinfusion of the coronary veins has also been used in larger animals yielding regional areas of transduction. In rodents, injection of an adenovirus carrying β-galactosidase into the pericardial sac transduced only the pericardial cell layers....[p. 617 bridging cols 1 and 2]." Overall, Hajjar et al suggests that the various approaches to delivering gene to the heart are limited in the efficacy.

The specification discloses a method of catheter-based delivery of the AOP-1 gene vector to the heart of a rat previously disclosed by del Monte et al (2001) (p. 48, [00151]). The specification also provides art of del Monte et al for more specific guidance to the methodology of a catheter-based gene delivery to the heart, therefore, providing enablement for a direct delivery to the cells of the heart by a catheter based delivery system in rat.

However, the instantly claimed invention is drawn to a gene therapy delivered by any method, and given the art described problems associated with the delivery of a vector to a target site by any other means than direct delivery, an artisan would look to the specification to overcome the art described obstacles. The specification only

provides specific guidance to a method of direct delivery to the heart via a catheter based system, therefore an artisan would not know how to use or make the instant method utilizing any other means to deliver the vector. Furthermore, for an artisan to carry out the claimed method they would have to determine means of overcoming the unpredictabilities described in the delivery of a vector by means other than the use of direct delivery and this would result in undue experimentation.

The instant invention is drawn to a method of administering an agent that encompasses a nucleic acid encoding AOP-1. However, for a gene therapy agent to be expressed effectively it must minimally comprise the elements to be directed by the transcription and translation machinery of the target cell which require a promoter capable of driving expression in the target cell. In the instant case, the specification discloses an adenoviral vector comprising the coding sequence for the AOP-1 gene operably linked to the CMV promoter and flanked on the 3' end of the AOP-1 gene a PolyA signal peptide. These elements resulted in the expression of AOP-1 in the heart when directly delivery to the heart. However, the instant claims only disclose "a nucleic acid encoding AOP-1". Because of the necessity for the minimal elements necessary to drive expression of a gene, an artisan would not know how to use a nucleic acid encoding AOP-1 without operable linkage to a promoter, in a gene therapy method that would result in the expression of the therapeutic gene. Furthermore, the claims are drawn to a prophylactic or therapeutic agent nucleic acid encoding AOP-1 (claims 8-14). However, again, an artisan would not know how to use the instant nucleic acid agent for its therapeutic use for the above described reasons.

The instant invention is drawn to the method of administering and agent that encompasses a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1. However, the specification and the art do not teach the elements of the nucleic acid sequence that are necessary to assure the expression of functional AOP-1. Therefore, an artisan would not know how to make a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 without have the design a significant number of sequence permutation, expressing the different variants, and then determine if they are functional. This level of experimentation would be considered undue.

The instant invention is drawn to the method of administering and agent that encompasses a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1. However, the specification does not teach any material with enhancing properties to the expression of the AOP-1 gene other than an exogenously introduced AOP-1 gene. Therefore, an artisan would not know how to make a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1 with out having to develop test systems that would first identify potential candidate materials for enhancing the expression, production, and function of AOP-1 and the further testing in vitro and in vivo to determine if the candidates actually enhance expression, production, and function of AOP-1. This level of experimentation would be considered undue.

The specification provides an effective use of an adenoviral vector delivery system to a rodent model of cardiac disease. The specification details several art accepted rodent models for cardiac disease. Hajjar et al also demonstrate delivery of a viral vector to the heart of healthy rodents (1998, 2000 and del Monte et al 2001). However, Hajjar et al also teaches, "Early proof of concept experiments in rodents will need to be extended to large-animal models with clinical-grade vectors and delivery systems to assess both efficacy and safety [p. 620, col 2, lines 5-7]." Hajjar et al also teaches that a catheter-based delivery of a viral vector to the rabbit heart in vivo using a method similar to their techniques resulted in less effective delivery of the vector to the heart and achieved predominantly epicardial transgene expression. [p. 617, col 2, lines 36-38]. Hajjar et al further teach, "Correlates of this method [their rodent catheter-bases delivery of a viral vector to the heart] in humans have not been established...Optimizing conditions for gene transfer in large animals and eventually humans will require substantial further investigation [p. 617, col 2, lines 44-45 and 48-50]". Hajjar et al also teach that the commonly used viral vectors in rodent models result in robust immune responses and therefore will likely require other vectors or further refined adenoviral systems for clinical application (p. 617, col1, par 2, lines 5-8). The problematic use of adenoviral vectors in humans is further supported by Chirmule et al (Gene Therapy, 6:1574-1583, 1999) who teach, "Most of this work [adenoviral gene therapy delivery] has been performed in animal models who are naïve to the virus. This will not be the case in humans, many of whom have been exposed to Ad or AAV due to a naturally acquired infection [p. 1577, sentence bridging col 1 and 2]".

Since the methods of the instant invention are based on the methods of Hajjar et al, and Hajjar et al suggests that these methods are unpredictable in other species besides rodents, the instant invention is also subject to these unpredictabilities. The specification does not provide further guidance to overcome the obstacles described by Hajjar et al. and others in the art; therefore an artisan would not know how to overcome the obstacles and unknowns described in the gene therapy art for any other species than rodent models. Furthermore, for an artisan to use or make the instant invention in any other in vivo model than rodents models, an artisan would have to test other vectors to determine is they are effective for delivery to cells in vitro, then determine if they are effective in transfecting cells in vivo, and then at least in the case of human, determine if the vector is safe for clinical use. This level of empirical experimentation goes beyond the bounds of routine experimentation and therefore considered undue.

The breadth of claims 1-14 includes prophylactic methods and agents, which encompasses treatment of a subject wherein the subject does not exhibit a disease state to prevent the onset of the disease state. The specification is not enabling for identifying a compound that prevents a condition because prevention or prophylaxis requires that the disease state be stopped before it has begun. The specification does not teach how to assess whether a subject will definitively acquire a condition of chronic heart failure prior to the subject exhibiting symptoms. Once a subject exhibits a phenotype, the methods encompassed by the claims would meet the qualifications for treatment, but not prevention. There are no teachings or guidance in the specification with regard to which subjects would be at risk for developing a phenotype such that the

phenotype can be inhibited prior to its onset or at what stage the claimed methods would be carried out to prevent onset of the phenotype.

Overall, the art of effective vector delivery to the heart, as disclosed above, is unpredictable. Therefore, an artisan would look to the specification to provide specific guidance to overcome these obstacles described in the art. The only specific guidance to overcome such obstacles of gene delivery provided are in reference to the method of Hajjar et al 2001. Therefore, an artisan would only know how to effective deliver a vector to the heart by the direct or catheter-based method described in the specification and art of Hajjar et al, therefore the instant invention is only enable for such disclosed methods of vector delivery to the heart.

Therefore, given the unpredictabilities in the art and the limited guidance provided by the specification, the specification only enables a method of treating chronic heart failure comprising administering to the heart of a rodent by direct cardiac injection or catheter-based delivery a vector comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said nucleic acid encoding AOP-1 in the heart of said rodent and while being enabling for a therapeutic agent for treatment of chronic heart failure comprising an active ingredient of a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said AOP-1 nucleic acid in the heart and wherein said nucleic acid enhances the expression and production of AOP-1, does not reasonably provide enablement for a prophylactic or therapeutic agent for a disease associated with decreased AOP-1 gene expression comprising: (1) transfecting cell of any affected tissue with any nucleic acid encoding AOP-1 or a

nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 by any means of delivery or (2) administering a material enhancing the expression of an/the AOP-1 gene, the production of AOP-1, or the function of AOP-1 by any means of delivery and does not reasonably enable a prophylactic or therapeutic agent for any disease associated with decreased expression of AOP-1 gene or AOP-1, comprising (1) any nucleic acid encoding AOP-1 or (2) any material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1.

Applicant traverses this rejection on the grounds (1) that the USPTO applied the wrong standard for enablement and that the invention need not be held to clinical standards to be enabled, (2) that the instant method can extend to other species than rodents and that Hajjar et al (1998) teaches that rat models are an appropriate animal model for studying gene transfer, (3) that the reliance of Hajjar et al (2000) is improper because it is directed to the efficacy and safety which is not a consideration in enablement, and (4) that the prophylactic or therapeutic method of the instant invention is applicable because it teaches the instant methods in a number of disease models.

Applicant's arguments have been fully consider and have not been found persuasive.

(1) Applicant's assertion that USPTO applies the standard of clinical readiness for enablement is not accurate. The Office Action mailed 8/9/2007, "at the time of filing,

the art of gene therapy for cardiac disease was premature for clinical use and many obstacles would need to be overcome before human trial were possible (Hajjar et al..." (see page 12). This statement was provided to broadly introduce that there are a great deal of unpredictabilities in the gene therapy art in particular when it comes to humans as the claims encompass. The rejection then continues to site more specific areas that result in the unpredictability such as the route of administration and the formidable barriers to administration that only enables direct delivery to the target cells and tissues (see p. 13) and the use of viral vectors (see p. 16) and issues of enablement such as the expression of a nucleic acid without a promoter to drive such expression (see p. 14-15) and the use of a method for prophylaxis (see p. 18).

The amendment to the claims did address some of the issues of enablement and not others. The amendment to the claims now encompass a direct delivery route of administration which generally is considered to be enabled. However, the claims recite, "administration by direct injection or catheter-based delivery....to cells of an individual" (see claim 1 lines 8-9). The breadth of this recitation encompasses delivering directly to any cell to treat chronic heart failure. Therefore, this suggests one could directly inject the vector into the cells of the eye, for example, and it will treat chronic heart failure. As previously stated in the Office Action mailed 8/9/2006, "the vector must be delivered to the affected tissue" (see last par, p. 13), in the instant case, the cells of the heart for the delivery to be considered direct. Therefore, the because the breadth of the claims still encompass an indirect route of administration, the method is still not enabled by the specification or art. The claims or the arguments by Applicant does not address the

unpredictabilities of viral vectors and the use of nucleic acid that does not have a promoter. Therefore, these issues of enablement are still encompassed by the claims.

Therefore, as suggested above, the issues of unpredictabilities and enablement, were not in fact, directed to issues of clinical use but issues make and use of the instantly claimed method and product as asserted by Applicant.

(2) Applicant assert that the method should extend to other species than rodents because the art teaches that the rat is an appropriate model for studying gene transfer. This argument is not found persuasive in part because the instant method are not claiming a method to study gene transfer but are claiming a method of treatment or prophylaxis, which have different considerations of enablement. For enablement of a gene transfer, one must demonstrate that a gene delivered and expressed in a target tissue. For a therapeutic gene therapy, one must additionally demonstrate that cells or tissue in need of treatment are treated. Therefore, Applicant's argument that the rat is an appropriate model for studying gene transfer is not applicable or persuasive. These arguments are also not found persuasive because as previously stated in the Office Action mailed 8/9/ 2007, the art of gene therapy in humans is premature and was many obstacles to over come (p. 12). The same Office Action also teaches from the art that the methods of catheter bases delivery of a vector was less effective in rabbits (see p.16). As previously states the art demonstrates unpredictabilities in at least to species of animals other than rats, and the specification does not provide specific guidance to overcome these unpredictabilities. Therefore, the specification is not enabling for all species of individual as is encompassed by the claims.

(3) Applicant's argument that the reliance of Hajjar et al (2000) is improper because it is directed to the efficacy and safety which is not a consideration in enablement is not found persuasive because the use of Hajjar et al (2000) is in the context of describing an unpredictability in the art. The Office Action does state, "Early proof of concept experiments I rodents will need to be extended to large-animal models with clininal-grade vectors and delivery systems to assess both efficacy and safety" (See page 16). This was stated to demonstrate that there are unpredictabilities in the art to overcome. The Office Action further states, "optimizing conditions for gene transfer in large animals and eventually humans will be required" (see page 17), further demonstrating unpredictabilities and specific guidance needed to use gene therapies in large animals and humans. Outside of the above recitation, the Office action does not discuss standards of safety or efficacy and therefore the Office Action was not judging the enablement of the instant invention on safety or efficacy, but on the grounds of unpredictability and the inability of the specification to provides specific guidance to overcome these unpredictabilities.

(4) Applicant's argument that the prophylactic or therapeutic method of the instant invention is applicable because it teaches the instant methods in a number of disease models is not found persuasive. First, the fact that the specification provides a number of examples of methods in different disease models does not seem to address the applicability of the instantly claimed method. The Office Action does acknowledge that a scope of a therapeutic method is enabled by the specification. In terms of a prophylactic method, the office action states, "...prophylactic methods and agents,

which encompasses treatment of a subject wherein the subject does not exhibit a disease state to prevent the onset of the disease state. The specification is not enabling for identifying a compound that prevents a condition because prevention or prophylaxis requires that the disease state be stopped before it has begun. The specification does not teach how to assess whether a subject will definitively acquire a condition of chronic heart failure prior to the subject exhibiting symptoms. Once a subject exhibits a phenotype, the methods encompassed by the claims would meet the qualifications for treatment, but not prevention. There are no teachings or guidance in the specification with regard to which subjects would be at risk for developing a phenotype such that the phenotype can be inhibited prior to its onset or at what stage the claimed methods would be carried out to prevent onset of the phenotype." (see page 18). However, the examples taught by the specification teach methods of induced conditions and not spontaneous conditions, therefore, it is unclear how these models demonstrate applicability to applicant asserts.

Newly added claims 33-38 specify that specific sequences for a nucleic acid encoding AOP-1 (SEQ ID NOS:1-3). These narrowing embodiments do not overcome the enablement rejections discussed above and in the original rejection set forth in the Office Action, mailed 8/9/2006. Therefore, these claims are also not enabled by the specification for reasons already set forth.

Therefore, because Applicant's arguments have not been found persuasive and the amendment to the claims have not addressed the enablement issue of route of delivery to a specific affected target tissue or cell, gene therapies applicable to other

species besides rodents, expressing a nucleic acid without linkage to a promoter, and prophylactic methods in spontaneous diseases, the claims are still not fully enablement for the breadth of the claims. Therefore, the claims still are only enabled for a method of treating chronic heart failure comprising administering to the heart of a rodent by direct cardiac injection or catheter-based delivery, a vector comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said nucleic acid encoding AOP-1 in the heart of said rodent and while being enabling for a therapeutic agent for treatment of chronic heart failure comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said AOP-1 nucleic acid in the heart and wherein said nucleic acid enhances the expression and production of AOP-1. Therefore, the enablement rejection of record is maintained.

***Claim Rejections - 35 USC § 112, 2nd Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. The rejection of1-7 and 9-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn.

Through the amendment and/or cancellations of claims, Applicant removed all recitations that were deemed indefinite. Therefore the rejection is withdrawn.

10. Newly added claims 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33-38 recite the limitation "said nucleic acid". There is insufficient antecedent basis for this limitation in the claim. Claim 1 and 8 recite two different nucleic acids (see lines 11-14 of claim 1 and lines 4-7 of claim 8). It is not clear to which nucleic acid dependent claims 33-38 are referring.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The rejection of claims 1, 3-7 and 8-13 under 35 U.S.C. 102(b) as being anticipated by Tsuji et al. (1995; of record), is withdrawn.

Applicant's amended the claims to recite "administering....to cells of an individual" which suggest administering to a multicellular organism, which E.coli is not. Therefore, the claims are no longer anticipated by Tsuji et al. Therefore, the rejection is withdrawn.

However, claims 8 and 14 stand rejected under 35 U.S.C. 102(b) as being anticipated by Tsuji et al. (1995; of record), as set on pages 21-23 for the in the Office Action, mailed 8/9/ 2006.

Applicant traversed this rejection on the applicant amended claim 1 and cancelled claims 3-7 and 9-13 which renders the rejection moot. Applicant's argument is not found persuasive because amended claim 8 and 14 are still pending which is drawn to a therapeutic agent comprising a nucleic acid ending AOP or a nucleic acid that hybridizes under stringent conditions to a complementary strand of a nucleic acid encoding AOP-1 and encodes a polypeptide that retains the function of AOP-1.

As previously stated in the Office Action, mailed 8/9/2006, Tsuji et al discloses cDNA sequences that encode human and mouse Mer5, also disclosed as AOP-1 gene. Therefore, Tsuji et al still anticipates the instant invention because all that is required is the nucleic acid encoding an AOP-1 gene to anticipate this product. Claim 8 and 14 also have some intended use language. However, when considering a product, intended use is not given patentable weight because the structure of the product is the same regardless of its intended use. Therefore, because Tsuji et al still anticipates claims 8 and 14, the rejection of claims 8 and 14 is maintained.

12. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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